

## **REMARKS**

Applicants respectfully request reconsideration of the rejections set forth in the Final Office Action mailed on January 9, 2003. Claims 1-41 are pending. Claims 5, 7-28, 30, and 32-36 have been rejected. Claims 1-4, 6, 29, 31, and 37-41 have been withdrawn from consideration. Claim 30 has been cancelled. Claims 5, 7-17, 32 and 34 have been amended. Claims 42-48 have been added herein.

This amendment is to expedite prosecution and should not be construed as acquiescence in any ground of rejection. Applicants reserve the right to prosecute the originally filed claims in the future. The comments in the Final Office Action are now addressed in turn.

### ***Claim Objections***

Claims 5, 7-11 are objected to since they depend from non-elected claims. Applicants have amended the claims herein accordingly to address this issue. Applicants request that the objection be withdrawn.

### ***Rejections Under 35 U.S.C. 102***

#### **WO 88/00474 and Geho 4,603,044**

Claims 5, 7-28, 30 and 32-36 have been rejected under 35 U.S.C. 102(b) as being anticipated by WO 88/00474 of record or Geho (4,603,044) also of record. The rejection is respectfully traversed.

Applicants agree with the Examiner in that Geho (4,603,044) and WO 88/00474 of record cite liposomes with Cr, Co, Fe or Zn complexed with iminodiacetic acid. However, these compounds employ water-soluble chelates which are of small molecular weight.

The present invention teaches the chemical composition of a polynuclear complex which is an exceptionally large polymeric molecule, having a much high molecular weight of 1948 as exemplified by its long crystalline morphology, ranging from 0.1mm to 0.3mm in length. The polymer is substantially water-insoluble; and consists of extended central repeating units represented by a polymerized octahedral structure, said structures being connected together by hydroxyl bridging groups.

Neither Geho nor WO 88/00474 describes an exceptionally high molecular weight water-insoluble polymer structure that bears any similarity to the present water-insoluble polynuclear complex. As the elements of Geho and WO 88/00474 are *not* the same as those claimed in the instant application, Applicants submit that Geho does not anticipate the pending claims and respectfully requests that this rejection be withdrawn.

#### **Bosworth**

Claims 5, 13, 22, 24, 32-33 and 35 have been rejected under 35 U.S.C. 102(b) as being anticipated by Bosworth (5,407,660). The rejection is respectfully traversed.

As repeatedly indicated by the courts, anticipation requires that all of the elements and limitations of the claim be found within a single prior art reference. There must be no difference between the claimed invention and the disclosure provided by the reference, as viewed by a person of ordinary skill in the field of the invention. (*Scripps Clinic & Research Fdn. V. Genentech, Inc.*, 927 F.2d 1565, 1576 [Fed. Cir. 1991]). Furthermore, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." (*In re Royka*, 490 F.2d 981, 180 USPQ 580 [CCPA 1974]). Applicants submit that Bosworth does not teach every element of the claims; therefore, that the invention, as claimed

herein, is not anticipated by Bosworth.

The present invention, as claimed herein, describes an exceptionally high-molecular weight water-insoluble polynuclear complex, never previously described or manufactured, that is composed of a specific chemical material which possesses the unique properties of specificity for hepatobiliary receptors. The high water-insolubility of the polymer also greatly facilitates the incorporation of said polymer into an organic mixture of the individual lipid constituents in order to promote commercial manufacturing and feasibility. A single sub-unit of the chromium complex targeting molecule features a Cr atom that is capable of accepting up to six ligands contributed by multivalent molecules, such as two molecules of N-(2,6 diisopropylphenylcarbamoylmethyl) iminodiacetic acid in media buffered by sodium acetate-acetic acid at pH 3.3. When the Cr metal is present, the metal moiety forms a repeated ionic bridge between the 2,6 isopropyl moieties, thereby minimizing the exposure of water attracting moieties such as the hydroxyl functionalities of the acetate groups and maximizing the effect of the water insoluble moieties such as the derivatized benzene ring structures, thus creating a polymer that is water-insoluble and of exceptionally high-molecular weight. This polymer has preference for the hepatobiliary receptors on the cellular hepatocytes in a warm-blooded host. The Examiner's attention is kindly directed to the results of tissue distribution experiments in mice, which demonstrate the hepato-specificity of the targeted liposome formulation (specification, p. 24).

The polynuclear water-insoluble complex of the instant invention precipitates and/or crystallizes from aqueous media and not from traditionally employed organic media. The polymerization of the organic-based polynuclear complex in an aqueous phase media occurs over the critical low pH of 3.2 to 3.3, which is substantially below the range of physiological pH. The properties of the resultant polynuclear material include an organic nature; an exceptionally high water-insolubility; a very large crystal-like structure, which exhibits crystals of orthorhombic morphology and substantial length of 0.1mm to 0.3mm and is represented by a repeated molecular uniformity that results in an exceptionally high molecular weight polymer. This polymer demonstrates significant solubility in organic solvents such as chloroform:methanol (2:v/v) and acetonitrile, and therefore greatly enhances the single-step addition and mixing of the extended polymeric complex with the other lipid constituents.

Bosworth makes no reference to the formation of an organic-based, water-insoluble polynuclear complex as described above. Conversely, Bosworth describes a water soluble agent that contains the chelate of a paramagnetic element such as iron, which is carried by or within or outside the external surface of a liposome. Bosworth states that the paramagnetic compounds themselves exhibit significant toxicity, but when rendered *water-soluble* through chelation, become relatively non-toxic. Thus, the increased water-solubility of the compounds is a prominent feature of Bosworth that serves to significantly decrease toxicity, and therefore, distinguishes from the water-insoluble complex of the present invention.

In addition, Bosworth teaches an agent in which the chelate of a paramagnetic element is carried to an organ or tissue by means of a liposome. Such preparations enhance NMR images of the reticuloendothelial system *in general*, citing the liver and spleen as target organs. Therefore, the compounds that Bosworth teaches feature no chemical components which impart a high degree of target organ specificity, particularly the hepatocytes of the liver.

As the elements of Bosworth are *not* the same as those claimed in the instant application, Applicants submit that Bosworth does not anticipate the pending claims and respectfully requests that this rejection be withdrawn.

#### Baldeschwieler

As indicated by the Examiner in paragraph 4, claims 5, 13, 15, 18, 22, 24, and 32-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Baldeschwieler (4,310,506). The

rejection is respectfully traversed.

Baldeschieler demonstrates the liposome delivery of diagnostic chelates containing metals such as Cr, In, Co and Zn with iminodiacetic acid, the liposomes containing the usual phospholipids. However, Baldeschieler does not suggest or teach a liposome with an insoluble polynuclear complex that exhibits the chemical property of being a hepatocyte-targeting molecule that fits into the liposome structure. Conversely, Baldeschieler teaches the liposome delivery of water-soluble chelates that are carried in the liposome's aqueous core.

As the elements of Baldeschieler are *not* the same as those claimed in the instant application, Applicants submit that Baldeschieler does not anticipate the pending claims and respectfully requests that this rejection be withdrawn.

### Conclusion

In conclusion, neither Bosworth, Baldeschieler, nor Geho describe a specific chemical material, which contains a polymer of high molecular weight, that is a water-insoluble, polynuclear structure of orthorhombic crystalline morphology that crystallizes and precipitates over the low pH range of 3.2 to 3.3 in aqueous media and exhibits the chemical property of being a hepatocyte-targeting molecule that incorporates into the liposome membrane. Conversely, the cited prior art teaches only water-soluble chelates of small molecular weight compounds.

The Applicants respectfully maintain that all pending claims are in condition for allowance. Therefore, the Applicants respectfully request a Notice of Allowance for this Application from the Examiner. Should any unresolved issues remain, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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